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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/002,413	01/02/1998	RICHARD C. ALLEN	311772000500	7792

25226 7590 08/28/2003

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/002,413	ALLEN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,42,44-46,48-50,55-57,62,63,65,66 and 68-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's arguments filed 6-13-03, paper number 39, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 remain pending and under consideration in the instant application as they relate to a method of administering cells to create an immunologically privileged site as originally elected.

Claim Rejections - 35 USC § 112

Claim 56, 57, 62, 63, 66 and 70-73 remain rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The limitation "wherein said RPE cells are allogeneic to the mammal" (claim 66) does not have support in the specification as originally filed. While the specification contemplates administering non-RPE that are allogeneic to the host using RPE cells provide immune privilege and increase survival time of the non-RPE in the host (pg 7, line 8 and line 28), the specification does not contemplate administering RPE that are allogeneic to the host or to the non-RPE cells.

Applicants argue claim 12 as originally filed supports the phrase because it states the transplantation is by allograft. Applicants' argument is not persuasive. Claim 12 as originally

filed does not support the phrase because it does not state the RPE cells are allografts or allogeneic to the mammal as claimed. Instead, the specification states the cells being administered with the RPE are allogeneic (pg 7, line 26).

Deletion of "allogeneic" describing the non-RPE in claim 56, 62 and 72 as amended is new matter. The specification does not contemplate combining RPE with any insulin producing, non-RPE as broadly amended. Applicants point to original claims 16 and 21, which describe a composition comprising RPE cells and cells that produce a therapeutic molecule. Applicants' argument is not persuasive. Claims 16 and 21 do not require non-RPE cells as claimed or that the non-RPE cells are insulin producing cells. Claim 22 as originally filed required combining RPE and insulin-producing β-cells (pg 4, line 33) or pancreatic islet of Langerhans cells. Claim 22 does not support combining RPE with any insulin-producing, non-RPE as broadly claimed because Langerhans cells are a specific type of cell and have a narrower scope than any "insulin-producing cell" which encompasses cells genetically modified to express insulin.

Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering a composition to mammal, said composition comprising retinal pigmented epithelial cells (RPE) and non-RPE, wherein said non-RPE cells are allogeneic to said mammal, does not reasonably provide enablement for increasing survival of the non-RPE in the mammal, producing a therapeutic

protein/biologically active molecule by administering the non-RPE or obtaining a therapeutic effect by administering the non-RPE. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The invention relates to administering allogeneic cells to a mammal using RPE such that an immune privileged site is obtained, protecting the non-RPE from the immune system of the mammal. The only disclosed purpose for administering the allogeneic cells is to treat disease by obtaining therapeutic levels of a biological molecule secreted by the allogeneic cells (pg 4, line 20).

The state of the art at the time of filing was that symptoms of Parkinson's disease were treated using RPE cells supported by a matrix transplanted into the brain of rats (Cherksey, see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). Cherksey did not expressly teach co-administering RPE and non-RPE cells, wherein the non-RPE were allogeneic to the host. However, Cherksey suggests transplanting a matrix having both RPE and allogeneic glial cells (column 9, line 2; column 11, line 37).

In addition, the art at the time of filing taught administering non-RPE into mammals to produce therapeutic molecules (Sigalla of record, Sept. 1, 1997, Human Gene Therapy, Vol. 8, pages 1625-1634; page 1626, column 2, 2nd and 3rd paragraphs; page 1628, column 1, 4th paragraph and column 2, 4th and 5th full paragraphs; Weber of record, 1997, J. Surg. Res., Vol.

69, pages 23-32; page 25, column 1, "Islet transplantation"; page 27, paragraph bridging columns 1 and 2; Fraser of record, 1995, Cell Transplantation, Vol. 4, pages 529-534).

While RPE were known to provide "immune privilege" (Ye of record, 1993, Current Eye research, Vol. 12, pages 629-639, see page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and page 631, column 2, line 20), the art at the time of filing did not teach the structure of a site resulting from administering RPE and allogeneic non-RPE to a mammal, define the immune response to such a site or teach how to increase survival of allogeneic non-RPE in a mammal using RPE. Therefore, it was unpredictable at the time of filing how to increase survival of allogeneic non-RPE in a mammal using RPE as claimed. Nor did the art at the time of filing teach how to obtain therapeutic levels of biological molecules produced by non-RPE protected within an immune privileged site created by RPE. Therefore, it was also unpredictable at the time of filing how to obtain therapeutic secretion of biological molecules produced by non-RPE protected within RPE cells.

The specification demonstrates isolating and culturing fetal RPE *in vitro* (pages 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE *in vitro* (pages 21-27). The specification suggests treating a number of diseases (page 1, line 23; page 3, line 26; page 5, line 31), delivering RPE to any of a number of tissues (page 15, line 7), administering RPE and non-RPE as a single composition or as separate compositions (page 4, line 23) and using non-RPE such as neural cells, endocrine cells, muscle cells and other cells that

produce a functionally active therapeutic molecule (sentence bridging pages 6 and 7). The specification does not teach administering RPE and non-RPE to a mammal, obtaining a therapeutic effect by administering RPE and allogeneic non-RPE or increasing the survival time of allogeneic non-RPE using RPE.

However, the specification does not enable administering RPE and non-RPE to a mammal, wherein the non-RPE are allogeneic to the mammal such that survival of the graft is facilitated or such that a therapeutic effect is obtained as claimed. A mere suggestion to increase the survival of allogeneic cells or to treat disease in a mammal by administering the allogeneic cells in combination with RPE is inadequate to overcome the unpredictability in the art to use the claimed invention to increase the survival of the non-RPE or to treat disease. The specification does not teach the structure obtained upon administering RPE and non-RPE, the immune response to such a site, the level of secretion of molecules produced by the non-RPE, or treating disease using such a method. The specification does not teach the immune response to such a site or rate of survival of the allogeneic non-RPE cells. The specification does not teach administering RPE and non-RPE to a mammal, wherein the non-RPE are allogeneic to the mammal. Therefore, the specification does not overcome the unpredictability in the art by teaching how to use RPE and allogeneic non-RPE to increase survival of the non-RPE or to secrete therapeutically effective amounts of a biologically active molecule from non-RPE in such a site.

Specifically, the specification does not provide any guidance on how to use allogeneic pancreatic islet of Langerhans cells (claims 57, 63, 73) or insulin-producing cells (claim 56, 62, 72) in combination with RPE to treat disease for reasons of record.

Applicants state the examiner doubts the truth or accuracy of the specification, and has not supported the rejection with reasoning or evidence. Applicants' argument is not persuasive. The examiner has established the state of the art of allogeneic transplantation with references and has gone through the Wand's factors to conclude that the specification does not enable one of skill in the art at the time of filing to increase the survival of allogeneic non-RPE cells in a host using RPE.

Applicants reiterate the art (pg 9-10) and the examiner's rejection but do not provide any reasoning why the art at the time of filing supports enablement of using RPE to increase the survival of allogeneic non-RPE cells in a host. For example, the examiner has already acknowledged the fact that non-RPE that produce a therapeutic protein had been administered into a host. However, it cannot be determined why such teachings enable increasing survival of non-RPE using RPE upon being administered to a host.

Applicants argue Selawry et al. (1993, Cell Trans., Vol. 2, pg 123) and Selawry (US Patent 5,725,854) support the claimed invention because they teach administering sertoli cells and pancreatic islet cells such that the sertoli cells create an immune-privileged site and the islet cells produce therapeutic levels of a biological molecule. Applicants' argument is not persuasive. The

specification does not provide adequate correlation between Sertoli cells and RPE such that similar results could be obtained. Pg 3, line 23, states Sertoli cells secrete FasL. The specification does not teach RPE secrete the same amount of FasL, that the structure of the site created by Sertoli cells and RPE is the same, that biological molecules secrete through a structure created by RPE or that the amount of secretion of a therapeutic protein obtained using RPE cells would be equivalent to that observed using Sertoli cells.

Applicants argue the references cited by the examiner do not support the unpredictability in the art. Applicants' argument is not persuasive. The examiner need not provide a reference that states the claimed invention cannot work. The examiner has established what was known and unknown at the time of filing. The dearth of information regarding how to use RPE cells to increase survival of allogeneic non-RPE cells makes the claimed invention unpredictable. The claims are not enabled because of the lack of guidance in the specification indicating RPE and Sertoli cells secrete the same amount of FasL, produce the same structure of an immune privileged site, secrete the same amount of therapeutic protein from the immune privileged site.

Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 65 remains indefinite because the preamble of the claim is not commensurate in scope with the body of the claim. The phrase "facilitating survival of an allogeneic graft" has a different scope than "increasing survival time" of cells that are allogeneic to the mammal. It appears that the preamble is intended to increase the survival time of all allogeneic cells that are administered to the host; however, the body of the claim only requires increasing the survival of the non-RPE cells. Applicants address the suggested claim language but do not address the rejection or address why the rejection is in error.

Claim 65 remains indefinite because it is unclear to what the survival time of the population of non-RPE cells is being compared. Is the survival time greater in the mammal than *in vitro*? Greater in the mammal using RPE as compared to administering the non-RPE cells alone? Greater than administering autologous non-RPE? As such the metes and bounds of when increased survival time of the non-RPE has been obtained cannot be determined. Overall, the result of administering RPE and non-RPE still cannot be determined. Applicants quote pg 4 and 7 but do not address how the citations clarify the claims or why the rejection is improper. The claims do not set forth to what the survival time is compared.

Claim Rejections - 35 USC § 103

Claims 41, 42, 44-46, 48, 49, 65 and 68-73 remain 68-71 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record.

Cherksey taught treating symptoms of Parkinson disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). RPE cells inherently secrete FasL and create localized immunosuppression (pg 2, line 27, of the specification). Cherksey does not teach co-administering RPE and non-RPE cells. However, Cherksey suggests transplanting a matrix having both RPE and glial cells attached (column 9, line 2) and that the glial cells may be allogeneic to the host (column 11, line 37). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer RPE and glial cells wherein the glial cells are allogeneic to the host as taught by Cherksey. One of ordinary skill in the art at the time the invention was made would have been motivated to add glial cells to the RPE as suggested by Cherksey and to treat neural disorders in the brain. The method of Cherksey increases "survival time" of the glial cells as compared to leaving the glial cells on the counter. The method of Cherksey increases "survival time" of the glial cells as compared to administering allogeneic glial cells without RPE because RPE inherently secrete FasL causing an "immune privilege site." Case law established that

reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

Applicants argue that Cherksey does not teach RPE cells secrete FasL to create an immune privileged site. Therefore, applicants argue Cherksey does not teach all the limitations of the claims. Applicants' argument is not persuasive. RPE cells inherently secrete FasL and create immune privileged site (pg 2, line 27). Cherksey need not teach the inherent feature of the RPE cells as claimed. Case law established that reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

Applicants argue that since Cherksey does not teach administering RPE cells with non-RPE cells to create an immune privileged site, one of ordinary skill would not be motivated to combine RPE and non-RPE cells. Applicants' argument is not persuasive because Cherksey clearly suggests administering RPE and adding non-RPE cells to the mixture.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER